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Our previous study found that chronic intermittent hypoxia (CIH) associated with recurrent apnea induced oxidative stress and inflammation in rat adrenal medulla. However, the underline mechanism was not clear. We hypothesized that, under CIH, the up-regulation of NADPH oxidase mediated by renin-angiotensin system (RAS) via an activation of angiotensin II receptor 1 (AT1) might take part in the oxidative stress and local inflammation in the adrenal medulla. Adult male SD rats were exposed to air (normoxic) control or CIH treatment (8 hours/day) which mimicked a severe recurrent sleep apneic condition for 14 days. Oral feeding of Telmisartan (10 mg/kg), a specific AT1 receptor blocker, or an intraperitoneal injection of apocynin (25 mg/kg i.p.), an inhibitor of NADPH oxidase, or vehicle was performed before the daily hypoxic treatment. The adrenal medulla was harvested for the measurement of markers for oxidative stress (MDA and NTR), macrophages infiltration (ED1), apoptosis, and inflammation (pro-inflammatory mediators) using TUNEL assay, real-time PCR, ELISA and Western blot. Levels of MDA and NTR were significantly increased in the hypoxic (CIH) group when compared with the normoxic control, but were normalized in the hypoxic groups treated with apocynin (AIH) or telmisartan (TIH). The expression levels of macrophage marker ED1-immunoreactivity and the pro-inflammatory mediators (TNFa, IL6) were also elevated in the CIH group, but were significantly ameliorated by the apocynin or telmisartan treatment. In addition, the amount of apoptotic cells in the CIH group was significantly higher than that of the AIH and TIH groups. Moreover, the mRNA levels of NADPH oxidase subunits (Nox2, Nox4) were increased significantly in the CIH group when compared with that of the AIH and TIH groups. Also, the protein expression of RAS components (AGT, AT1) was also increased in the CIH group. In conclusion, we showed that an up-regulation of NADPH oxidase via AT1 receptor activation mediates CIH-induced oxidative stress and inflammation in rat adrenal medulla.

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REDUCTION IN HEPATIC APOPTOSIS MODULATED BY GARLIC DERIVED S-ALLYLMERCAPTOCYSTEINE (SAMC) IN NON-ALCOHOLIC FATTY LIVER DISEASE RAT MODEL THROUGH P53-DEPENDENT PATHWAYS

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Purpose Previous study demonstrated that administration of garlic-derived antioxidant S-allylmercaptocysteine (SAMC) ameliorated hepatic injury in a non-alcoholic fatty liver disease (NAFLD) rat model. In the present study, we investigated the effect and mechanism of SAMC on NAFLD-induced cellular apoptosis in the liver.

Methods Adult Sprague-Dawley female rats were fed with a diet comprising of highly unsaturated fat diet (30% fish oil) for 8 weeks to develop NAFLD with or without intraperitoneal injection of 200 mg/kg SAMC three times per week. After chemical euthanasia, liver samples were collected for histological, biochemical and molecular analyses.

Results During NAFLD development, increased apoptotic cells were observed in the liver. Hepatic apoptosis was accompanied by activated intrinsic apoptotic pathway as shown by expressional changes of cytochrome c and Bcl-2 family genes. Extrinsic apoptotic pathway was also activated as shown by expressional changes of Fas, TRAIL, FADD and cleaved caspase-8. Increased activity of caspase-3 further confirmed the activation of apoptosis. In addition, reduced activity of LKB1/AMPK and PI3K/Akt pathways could be observed with increased expression of pro-apoptotic regulator p53 in NAFLD rats. Administration of SAMC reduced the number of apoptotic cells through down-regulation of both intrinsic and extrinsic apoptotic mechanisms. Phosphorylation status of LKB1, AMPK, PI3K, and Akt were also restored by SAMC co-treatment, leading to the reduction of p53 expression.

Conclusion Administration of SAMC during NAFLD development in rats protects liver from apoptosis through p53-dependent intrinsic and extrinsic apoptotic pathways.